DISCUSSION

NELSON J. HOWARD, M. D. (350 Post Street, San Francisco).—None of us will disagree with Doctor Schmoele in regarding injection thrombosis as the treatment of choice in dealing with varicose veins. It is very important for every practitioner to have in mind the altered physiologic and anatomic factors present in this condition, and so well summarized by Doctor Schmoele, in order to be able to treat competently the varied pathologic stages presented by the individual varicose patient. The gravity method of relief of venous stasis and tissue edema is a very valuable one and, as emphasized by Doctor Schmoele, does not take the place of compression bandage therapy, but supplements it. The use of the rubber or sea sponge beneath the elastic compression is not necessary, in my experience, if *sufficient* and *continued* elastic compression is maintained. Unna's paste boots applied to the huge, soggy, edematous limb without compression, fail to accomplish a cure of the ulcer. Previous elevation of the limb and gravity reduction of the edema, followed by the application of a Kleebro elastic adhesive bandage (or less comfortable, an Ace elastic bandage), and reinforced by repeated layers of Unna's paste, gives good continued sufficient elastic support to allow the ulcer to heal. It goes without saying, that the veins should receive thrombosing injections.

I do disagree with Doctor Schmoele in his use of the term "malignant ulcer," which, with accuracy, should be reserved for actual neoplastic changes arising in the scar of a healed ulcer, or in the unhealed margins of a long-existing chronic ulcer. My own belief is that every varicose ulcer can be healed, except those in which the deep veins are of insufficient caliber, and in which repeated thrombosis prevents sufficient recanalization to restore an adequate lumen for return of blood to the body. Edema, ulceration and infection may exist, but as long as the deep veins are sufficiently patent, competent or incompetent, I feel the ulcer can be healed by simple means. Long duration of the ulcer, presence of edema and eczema are no bar to success, and these cases cannot justly be said to possess a malignant ulcer. Huge ulcers, unhealed for 40, 31 and 22 years, with brawny edema and eczema, but with patent deep veins, have responded with healing in eight weeks or less, if obliteration of superficial veins is combined with adequate continued elastic support. Operation and skin-grafting were found unnecessary. Doctor Schmoele rightfully emphasizes the necessity of testing for *sufficiently* deep vein patulousness. In ulcer cases, with occlusion of the deep set of veins, I have not as yet found a satisfactory method of treatment.

A real advance would be secured if the medical profession as a whole would attempt the prevention of varicose veins. Varicose veins have no common cause. In certainly a third of the patients, they first are manifest in adolescent or early adult years, presumably through a congenital type of variation in vein-valve development. However, the thrombophlebitis following childbirth, operation, infectious diseases and trauma, are followed in a surprising number of cases by varicosities. Early and continued use of elastic support of the limbs of those patients with thrombophlebitis or edema is imperative, whether the condition follows childbirth, operation, or trauma. Adequate support to the superficial saphenous system, from the moment the patient is ambulatory, prevents the increase of edema, accelerates the recanalization of the deep thrombi, and tends to prevent or minimize future development of varicosities of the superficial saphenous system.

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E. VINCENT ASKEY, M. D. (1930 Wilshire Boulevard, Los Angeles).—The injection treatment of varicose ulcer and veins has received, deservedly, so much discussion in the past few years that a simple understandable presentation of the factors involved and the treatment now in use is of practical value.

Doctor Schmoele has outlined in clear language the problem—the necessary Trendelenberg and Perthe tests (which are so often unknown to or neglected by the physician with little experience in this problem), and he has given the exact technique and the precautions to be observed, so that I feel therein lies the value of his paper. It is concise, definite, inclusive.

Doctor Schmoele's procedure, of regular hourly elevation of the leg in the treatment of "malignant" ulcer, I feel is a worthwhile innovation in that it avoids absolute inactivity and allows the patient to be ambulant. The morale of the patient and his coöperation will be increased because he will feel that something definite and of great importance is being done which he can see and of which he is a definite part. The psychology of this in itself is of value, and this procedure could be adopted with profit by all of us in the treatment of this condition.

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NORMAN J. KILBOURNE, M. D. (2007 Wilshire Boulevard, Los Angeles).—The author is correct in advising pressure with the rubber sponge instead of the now antiquated Unna's paste boot. He is also right in the use of a dry dressing. Strips of cellophane paper across the wound will keep the dressing from sticking. This is a better treatment than the use of the many ointments.

In the treatment of ulcers associated with chronic infection of the lymphatics, hot compresses are helpful.

When there is a question as to whether pain in the legs is due to varicose veins or fallen arches, it is more likely to be due to varicose veins. However, certain cases, in which pain persists after injection of veins, will be relieved if referred to an orthopedic man for arch support.

Solution of sodium morrhuate is valuable in small veins where there is a possibility of extravasation, for the sloughs due to extravasated sodium morrhuate will heal more quickly than sloughs due to extravasated quinin. Sodium morrhuate is a soap which is so very variable in composition that potassium oleate is preferable. Potassium oleate is a similar soap, which is not only cheaper but definite and of invariable composition and effect.

In cases where there is a history of phlebitis and also in large veins with increased danger of phlebitis, quinin urethane solution is still preferable because it is bactericidal. The quinin remains in the tissues for more than five days and so affects the surface tension on the outside of the leukocytes that it prevents phagocytic action which might loosen the thrombus. Potassium oleate with a small amount of quinin added is now available. The author's attitude on ligation of the saphenous vein is correct.

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# PIGMENTATION OF METABOLIC ORIGIN: ITS RELATION TO THE AUTONOMIC NERVOUS SYSTEM*

*By* IRVING BANCROFT, M.D.
*Los Angeles*

DISCUSSION *by H. P. Jacobson, M.D., Los Angeles; Sophie A. Lurie, M.D., Los Angeles; George V. Kulchar, San Francisco.*

THIS discussion is intended to be limited to the influence of the autonomic nervous system on abnormalities of pigmentation. The influence of light on pigmentation will not be touched upon. Neither will the causes of various hematogenous pigmentation be gone into. An attempt will be made to explain certain facts about metabolic pigmentation and the formation of melanin.

## ORIGIN OF PIGMENT

Certain types of pigment definitely originate in extravasated or stagnant blood, but melanin definitely does not originate from the blood. It contains neither sulphur nor iron, which are essential elements in blood. Moreover, Eirowsky[1] has shown that melanin production can occur in portions of skin which have been cut off from the general circulation, and also in Thiersch grafts *in vitro*.

* Read before the Dermatology and Syphilology Section of the California Medical Association at the sixty-fourth annual session, Yosemite National Park, May 13-16, 1935.

Block and other German workers have devised some very complicated theories based on experimental facts, which are essentially as follows: The cells which are capable of producing melanin, or which contain melanin, are confined to the basal layer and to the deeper portions of the rete malpigii in light-colored races. These cells contain a chemical substance which is capable, under certain circumstances, of being so acted upon that melanin particles are deposited in the upper part of the individual cell. This reaction can take place artificially *in vitro* as well as naturally in the body. The synthetic chemical substance which is capable of bringing this about is called "dopa," and the word is derived from the first letters of a complicated organic compound. Dopa is a derivative of tyrosin, and if it is left in contact with frozen sections of human skin, certain cells of the basal layer become darkened, and this darkening corresponds with the degree of pigmentation of the skin which is used in the experiment. The same phenomenon occurs if dopa is incubated with human skin. But if the skin is heated, or if low concentrations of cyanid are allowed to be in contact with the skin, no dopa reaction or darkening takes place. This would seem to indicate that an enzyme is concerned in the process. In the skin of an albino, or in that taken from an area of vitiligo, no dopa reaction takes place. In other words, the elements capable of making melanin are absent from that area. The cells which are capable of developing melanin are called melanoblasts, and their number varies in different races, individuals, and localities.

## AUTONOMIC NERVOUS SYSTEM

Briefly reviewing certain familiar facts about the autonomic nervous system, you will recall that the sympathetic nerve system is that section of the autonomic nervous system which arises from the dorsal nerves. This section of the autonomic system is distributed to all the smooth muscles and glands of the body. When it meets nerves from the cervical and lumbar sections of the autonomic nervous system in any organ or gland, its action is opposed to that of the local nerve. When this balance is perfect, the parts served are in a normal state; but when one set is stronger, a state of malfunction exists. This state of malfunction is often local and temporary, or may, in certain cases, be permanent. Temporary ascendancy of one or the other opposing nerves is dependent directly on emotions, and is usually not subject to voluntary control.

Anatomical and physiological researches show that all glands have a very rich nerve supply which comes from the autonomic system, and that changes in glandular activity are dependent upon stimulation of the accelerator or depressor branches of the autonomic nervous system.

## INFLUENCE OF THE GLANDULAR SYSTEM ON PIGMENT FORMATION

The influence of the glandular system on the formation of pigment is not definitely known, but it is generally understood that the pituitary, adrenal and thyroid glands, at least, have some influence on the formation of pigment; and it is also generally understood that these three glands have a definite relation to each other. If thyroidectomy is performed, the pituitary gland increases in size, and if certain hormones obtained from the pituitary gland are injected into an animal, the epinephrin content of the adrenals is reduced.

*Adrenal Glands.* — From the medulla of the adrenal gland may be extracted a substance commonly called epinephrin, which has most extraordinary qualities. It stimulates the sympathetic nervous system just as though it were stimulated by nervous impulse. If injected into the blood, it causes blood sugar to increase, even to the point of glycosuria, the pupils to dilate, the blood vessels to contract, and the hair to stand erect. Even after the organs are removed from the body and kept in salt solution, the same effect takes place. It may be demonstrated by its action on the muscle of rabbits in amounts as small as one part in two hundred million (Cannon),[2] and on the heart muscle by one part in 1,400,000,000 or one drop in 22,786 gallons.

Diminished adrenal secretion, as observed in Addison's disease, is always accompanied by abnormal pigmentation which varies in color from light yellow to brown, or even black. The physiological explanation of this hyperpigmentation is that the defective adrenal glands fail to remove the substance in the blood which is the normal precursor of epinephrin, and that, as a result of this failure, there is an abnormal amount of this substance in the blood, and it acts just as dopa does. In fact, it is probable that it is identical with dopa in chemical composition.

*Thyroid Gland.*—Abnormal pigmentation sometimes occurs in hyperthyroidism, and according to Perrin[3] even regresses parallel with the decrease of thyroid secretion, and after thyroidectomy it disappears in a few days. The abnormal pigmentation which I have observed in hyperthyroidism is diffuse and not marked, and limited to the upper part of the chest and neck.

*Pituitary Gland.*—The pituitary gland, which physiologists tell us weighs about ten grains, also has some connection with pigment formation. It has a definite influence on the chromatophores of cold-blooded animals, and injection of an extract of the pituitary has the power to quickly cause color in those animals to darken. The amount of hormone which causes a deep red color to appear over a certain small area is called a phoximus unit, and is used as a definite measure of the melanophore stimulating hormone. Lack of this hormone in lower animals also causes loss of pigment. Beyer[4] cites a case in which an especially light-colored frog was found to have a pituitary gland in which the pars intermedia was entirely destroyed by a peculiar parasite.

## COMMENT

Cannon and Brittan[5] showed, by the following experiment, that adrenal secretion was definitely dependent on the sympathetic nervous system. A cat, whose heart had been completely denervated, was confronted by an aggressive dog, and re-

sponded by all signs of anger, including standing of hair and acceleration of the heart beats by as much as fifty beats a minute. Afterward, the same experiment was performed, but the adrenal glands were inactivated: this time the heart beat did not increase in rate at all, or in some cases not more than two beats a minute.

Eliot [6] stated that the iris of a cat's eye, after being deprived of its sympathetic nerves, was dilated more widely than normal when it became angry, and that this effect failed to occur if the adrenal glands were removed.

Clinical facts regarding the rôle of emotion as a factor in sympathetic unbalance are less definite than animal experimentation, but nevertheless are noteworthy. Maranon [7] has collected an extensive series of cases of hyperthyroidism brought on by war experiences. Emerson [8] cites a case in which "the fiancée of a young man pretended to commit suicide in his presence. He departed hastily, and within a week had a swelling of his thyroid region and was nervous. Four months later he presented a large goiter, and his basal metabolism was up 24 per cent."

Cannon [9] also states definitely that emotional shock is sometimes followed by permanent diabetes.

### REPORT OF CASES

CASE 1.—One of the most marked personal experiences of that sort was that of a boy of nine who, for punishment, was put in a closet one Friday afternoon by his teacher. She went home and forgot him until late that night. Soon after this, he developed vitiligo and his hair turned iron-gray. His mother said that his hair turned gray the next morning, but I did not see him for several weeks, and that statement is of questionable veracity.

CASE 2.—Another example is that of a man of fifty-two, who for years had had vitiligo. His son was killed in an automobile accident, and soon after this he lost his hair permanently.

CASE 3.—Another young man had alopecia areata, from which he had practically recovered. He was later in the Long Beach earthquake, and in a few days the alopecia returned, more extensive than ever.

CASE 4.—Another man was thrown twenty feet by an automobile, and within a week developed lichen planus.

### COMMENT

The susceptibility to unbalance of the autonomic nervous system seems in some ways to resemble that of insanity. Families or individuals have a tendency to autonomic unbalance, and this unbalance may come spontaneously or be induced by some upsetting condition. I have noticed that vitiligo is frequently met in relatives. Giljarowski [10] found seven cases of alopecia areata among 293 mental cases, and Jordan [11] found two cases of vitiligo among ninety-one cases of alopecia areata. In addition to family or individual tendency to insanity or emotional unbalance, emotional strains act at times to induce both of these conditions.

Complete loss of pigment in deeply pigmented races is not unknown.

### REPORT OF CASES

CASE 5.—A Los Angeles negro, who presents photographic proof of his normal color at the age of eighteen, is now entirely white except for an area of about one square inch. He seems to be normal, except that he had an injury to his forehead when he was a child.

CASE 6.—Another Los Angeles resident of Mexican ancestry has lost all her pigment, but no cause can be found, as she seems to be normal in every way, and her disease seemed to act like an extensive case of vitiligo.

### CAUSES OF ENDOCRINE UNBALANCE

In addition to emotional shock or nervous strain as a cause of endocrine unbalance, one might place under suspicion: (1) syphilis; (2) toxins; (3) chemical poisons.

These may work by causing disease of some sections of the autonomic system, or by causing a susceptibility to unbalance; and in the case of syphilis, by action on the gland tissue itself.

Syphilis is a possible cause of sympathetic unbalance, especially congenital syphilis. Congenital syphilis may cause a fibrosis of glands which produce a deficiency of secretion rather than direct action on the sympathetic system. I have seen recently a man of thirty-eight who had syphilis in 1922 and vitiligo in 1927; but, as a rule, I have not found syphilis and vitiligo to be definitely connected. Von Recklinghausen's disease also sometimes gives hyperpigmentation, and probably does this by direct destruction of nerve tissue.

Diseases such as diphtheria, typhoid and tuberculosis may cause adrenal deficiency by direct action, and also by action on the sympathetic system. I recently saw a man of forty-eight who had typhoid when he was nine years old. Soon after that he had vitiligo and lost all his hair, which returned, but white in color. After several years it turned black, but he still has marked vitiligo.

Arsenic is the chief chemical poison which causes hyperpigmentation, and it probably causes this by direct action on the melanoblasts and not by any action on the autonomic nervous system. In fact, most hyperpigmented areas are caused by direct action on melanoblasts. Chronic friction, light, and certain inflammatory conditions are examples of this. Still, arsenic is also a possible cause of autonomic unbalance. It is my opinion, unsupported by figures, that I have seen herpes zoster and lichen planus frequently during the administration of arsenic, and, in isolated instances, urticaria, angioneurotic edema, scleroderma, and Raynaud's disease, which are all diseases in which the autonomic nervous system has some part in the etiology.

### SUMMARY

Arsenic is the chief cause of local hyperpigmentation, but sometimes unbalance of the autonomic nervous system results in abnormal pigmentation. The autonomic nervous system may be thrown out of balance by violent emotion, by syphilis, by toxins of certain diseases, and by chemical poisons.

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DISCUSSION

H. P. JACOBSON, M. D. (2007 Wilshire Boulevard, Los Angeles).—I am in complete accord with the views so concisely expressed by Doctor Bancroft, though I am well aware of the fact that the available supportive evidence is meager indeed.

The thesis of a probable endocrine-sympathetic-pigmentary relationship is not a new concept. The idea has been expressed a good many times before by clinical and experimental investigators in the fields of biology, physiology, and biochemistry. Supporting this theory of relationship is the well-known experimental observation that early removal of the hypophysis in the frog tadpole results in the production of a species with a greatly disturbed pigmentary system—the so-called silvery or albino individual. Then, again, it has been demonstrated that post-pituitary extract is capable of effecting a darkening in color of these albino tadpoles. Furthermore, when immersed in post-pituitary lobe-extract solutions, the pigment cells of the frog's iris expand and become darker.

The importance of the adrenals and thyroid gland need hardly be stressed here, except to point out the view that the cortical portions of the adrenals are probably more intimately concerned with the metabolism of pigmentation than are the medullary parts. It might also be added that the sex glands, too, probably bear some sort of a relationship to the biochemistry of pigmentation, as may be judged from the well-known clinical dermatologic pictures of the various types of chloasma—dysmenorrheic, pregnancy, and climacteric. Whether in these clinical states (chloasmas) the pathologic physiology is limited to the sex glands alone, or there is, in addition, an adrenal cortical factor, is at present an open question. It seems reasonable to presume, however, in the light of the supposed relationship that the members of this chain of glands seem to bear to one another, that in the chloasmas, as in all other pigmentary clinical syndromes, the spirit of coöperation governs their collective functioning. Thus, for instance, in the chloasmas, the glands primarily concerned in the disturbance are probably the sex organs, while the adrenals, pituitary, etc., play a secondary rôle. On the other hand, the characteristic bronzing in Addison's disease is primarily a result of diseased adrenals, though the other members of the chain are probably also affected secondarily. Again, the not uncommonly observed pigmented warts and plaques on acromegalic patients are, *a priori,* clinical expression of pituitary disease, though the thyroid and adrenals probably play a minor, albeit a definite part in the syndrome. Similarly the various forms of abnormal pigmentary manifestations so frequently observed in thyroid disease are probably a result of disturbed functioning of this gland, plus a secondary involvement of some of the other glands.

There seems to be a fair agreement among students of endocrinology that, normally, there exists an harmonious interrelation in the working of these glands, and that an abnormal functioning of one ultimately affects the physiological balance of all the others in the group.

Regarding the influence of the autonomic systems on the endocrines, and on the processes of metabolic pigmentation, little need be added to what has already been said. You will recall, for instance, that stimulation of the splanchnic nerves by any one of a number of stimuli (mechanical, chemical, mental, or emotional) results in an increased discharge of adrenalin by the medullary portion of the adrenal on the stimulated side. Conversely, sectioning of the splanchnic nerve supply to a given adrenal results in a marked diminution or complete stoppage of adrenalin output on that side.

Animal biologists tell us that certain animals are able to change their color from light to dark, or vice versa, according to the color of their environmental background. They explain this phenomenal ability of the animals on the basis of sympathetic action, by assuming that the color of the background, acting upon the sympathetics via the eyes, causes the chromatophores to expand or contract, and the animal thereby changes its color. In support of this assumption may be cited the fact that blind frogs and fish have lost their power to change color.

From the clinical standpoint we all know, for instance, that fright, worry, shock, and other types of emotional upsets are not infrequently productive of such clinical conditions as premature graying of hair, vitiligo, etc.; and it need hardly be stressed that even more so than emotional upsets, biochemical toxins and poisons may, and not infrequently do, act directly and banefully upon the endocrine and autonomic systems and cause various types of pigmentary disturbances.

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SOPHIE A. LURIE, M. D. (1025 Story Building, Los Angeles).—Is it not reasonable to speculate on the idea that syphilis attacks any gland of the system, and thus impairs or destroys its function? Clinical observations have shown us that syphilis of the pancreas produces manifestations of diabetes, which responds favorably to anti-luetic treatments.

We have seen also a case of congenital syphilis with a low basal metabolic rate when the thyroid gland was affected by syphilis. This responded spectacularly to anti-syphilitic treatment instead of specific endocrine therapy.

We presume that it may be worth while to think of the analogy of the above-mentioned facts, that, when the adrenals are attacked by the syphilitic process, vitiligo might be one of the clinical manifestations as a dysfunction of the regulation of pigment distribution. Considering the fact that our patients are asthenic to a greater or lesser degree and respond very impressively to bismuth salicylate intramuscular injections, we are inclined to believe that syphilis of the adrenals may be linked with the problem of vitiligo.

Five children of the Yale Street Health Center of Los Angeles are doing very well under bismuth salicylate intramuscular injections, combined with generalized quartz-light therapy; they are instructed to expose themselves to the sun.[1]

One of the patients (a thirteen-year-old girl) has had an area of vitiligo on the right cheek, in front of the ear, from birth, with a four-plus Wassermann. The rest of them have shown negative Wassermanns of the blood. The spinal test has never been taken.

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GEORGE V. KULCHAR, M. D. (450 Sutter Street, San Francisco).—The studies of Bloch, Peck, and others, have given us an understanding of the cellular mechanism of pigmentation, but as yet there is no physiologic demonstration of the agency or agencies which control the processes of melanotic pigmentation in the skin. The causal relation between disturbances of pigmentation and the endocrine glands has been a frequent clinical observation, but we do not know if this action is caused by pathologic changes in the secretions of these glands or, in an indirect way, by the alteration of their vegetative nervous system control. There is a mass of evidence to indicate that the adrenals and the pituitary play an important part in the control of pigment metabolism. Recently Zondek has reported the presence of a melanophore-stimulating hormone in the pars intermedia of the pituitary. This hormone has been shown to be present, likewise, in the walls of the third ventricle, where the centers for the vegetative nervous system are located; attempts to demonstrate its presence in other parts of the body, except

[1] Elsewhere we have mentioned the principle of this treatment. (C. F. *Archives of Dermatology and Syphilology,* February, 1935. *Transactions of the Los Angeles Dermatological Society,* May 8, 1934.)

for small quantities in the blood stream, have to date been unsuccessful, a most interesting observation in the light of the vegetative theory of the nervous system control of the processes of pigmentation.

Addison's disease is, of course, the classic example of pigmentation following glandular insufficiency. However, in not all of the cases can actual histologic changes be detected in the adrenals. In a few cases the lesions are in other parts of the chromaffin system, such as the paraganglia and sympathetic ganglia, all derivatives of the sympathetic nervous system. Cases are reported following destructive lesions of these autonomic nervous-system structures, caused by carcinomatous invasion, tuberculosis, syphilis and bacterial infections and drugs, particularly the arsphenamins.

The supposition is that these patients have a congenital insufficiency of their chromaffin system which makes it more susceptible to injury. Whether this hypothesis is true or not, certain it is that interference with the secretory nervous supply of the suprarenal will result in melanotic pigmentation of the skin and mucous membranes.

Epinephrin, a product of the chromaffin tissues, seems to be in some integral way connected with the deposit of melanin in the skin. We know that epinephrin is closely related to tyrosin, a chromogenic substance, capable of producing pigments. The supposition is that, if the adrenal is functioning normally, the tyrosin is converted into epinephrin; but in case of hypofunction of the suprarenals, the tyrosin is unable to break down any further, and this may result in pigmentation.

Just a word as to the local processes of pigmentation. The hyperpigmentation, resulting from disturbances of the endocrine system, arising from lesions within the glands themselves, or, secondarily to interference with their autonomic nervous supply, appears to be merely a quantitative increase in the normal processes of pigmentation. The activity of the melanoblasts is greatly increased. Many more cells participate in the action, and the basal layer histologically appears a black band from which many dendrites ascend. However, the fundamental process of melanogenesis appears to be unchangeed.

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# RESULTS OF TREATMENT OF CONGENITAL LUETICS WITH BISMUTH ARSPHENAMINE SULFONATE (BISMARSEN) FOR FIVE YEARS*

*By* WILLIAM ANTHONY REILLY, M.D.
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DISCUSSION *by Hartzell H. Ray, M.D., San Mateo; Merlin T.-R. Maynard, M.D., San Jose; Stanley O. Chambers, M.D., Los Angeles.*

BISMUTH arsphenamin sulfonate, hereafter referred to by the trade-name "Bismarsen," has distinct advantages for the treatment of children suffering from congenital lues. It is given intramuscularly with less effort for the physician, and discomfort for the patient, than is an intravenous antisyphilitic drug. The local and general reactions are much less frequent and severe. The toxicity is less than from such common antisyphilitics as sulpharsphenamin, neoarsphenamin or mercurials, and the therapeutic effectiveness is very high. This means that children will be more faithful to therapy and good results can be achieved. Stokes and Raiziss[1] (the latter the originator), and Chambers,[2] have reviewed the chemical constitution and pharmacological properties of the drug.

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Read before the Dermatology and Syphilology Section of the California Medical Association at the sixty-fourth annual session, Yosemite National Park, May 13–16, 1935.

## CLINICAL MATERIAL FOR THIS STUDY

The use of Bismarsen was initiated in our Pediatric Clinic in 1930, as part of a coöperative study with Chambers. Many acquired cases in adults have been treated with this drug, but few cases of congenital luetics have been reported. Chambers and Koetter[3] observed a group of 180 children for from one and a half to two years, who had received over 6,000 injections, which is the largest and most comprehensive study. Our group comprises 170 children ranging in age from birth to sixteen years, observed for five years and having had over 3,200 injections. Our technique differed from that of Chambers and Koetter, since we were able to treat these patients only once a week, while their patients were treated twice weekly.

## RESULTS

*Reactions.*—Reactions occurred twenty-six times, or less than 0.8 per cent, and twenty-two, or 90 per cent of the reactions were immediate, eighteen being nitritoid only and four also having purpura. The purpuras occurred twice in two patients, and in the only examination done, there was not a reduced platelet count. The nitritoid reactions were not very severe and were readily controlled by epinephrin. The Zarisch-Herxheimer reaction occurred once, two years after the patient started treatment with this drug. No reactions from bismuth were encountered. The infrequency of reactions, and their relative mildness, are two of the advantages of the use of the drug.

*Toxicity.*—The 12 to 15 per cent of arsenic in the arsphenamin and the 25 per cent of bismuth in the compound, make it necessary to watch for skin, liver, kidney, blood and peripheral nerve effects. Such were extremely uncommon. Two patients had a very mild albuminuric nephritis, which rapidly cleared. The reactions noted above might be added as toxic manifestations, especially the purpuras in two patients. One patient was desensitized successfully without a recurrence of the purpura. There were no instances of arsenical anemia, dermatitis, neuritis, or enteritis. This also applies to the less frequently encountered bismuth poisoning. The rarity of toxicity is another advantage of this drug.

*Effects on Lesions.*—Congenital lues in this locality is usually latent and tertiary, due to the widespread treatment of pregnant mothers. The clinical signs and symptoms are few (about 16 per cent of patients), and the diagnosis depends mainly on the serology.

Infants with secondary manifestations of a very active nature are usually difficult to treat with any drug. Bismarsen seemed to be less toxic to them, if given in very cautious doses beginning with 10 milligrams, and apparently controlled the dissemination of the spirochete very well. Only two such cases were fatal in a group of ten. Table 1 shows the favorable reactions the drug has on the lesions at all ages. Skeletal lesions healed rapidly and well, except in fatal cases. This applies in a lesser degree to skin and mucosal lesions. One infant with snuffles was very slow to heal, and required about two months. Eye lesions, mainly